DIAGNOSIS AND TREATMENT OF LYME DISEASE

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: May 1, 1991
Application Receipt Date: June 17, 1991

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invites applications for grants to conduct research on the diagnosis and treatment of Lyme disease.

BACKGROUND

Lyme disease is a spirochetal disease, usually transmitted by the bite of a tick, most often by a nymphal Ixodes dammini, when this species is prevalent in the Spring.
Subsequent to its first description in 1975, Lyme disease has become the most common tick-borne illness in the United States, with approximately 8,800 new cases reported in 1990.
Endemic areas in the United States include the northeast, north central, and western regions.

The spectrum of manifestations resulting from Lyme disease ranges from the initial skin lesion, erythema migrans, in approximately 60 percent of all cases, to chronic arthritic and neurologic disability. Symptoms of different organ systems (skin, heart, nervous system, eye, and joints) are often combined.

Some researchers have distinguished three separate disease stages: Stage I, characterized primarily by erythema migrans and flu-like symptoms; Stage II, differentiated by dermatologic, ophthalmologic, neurologic, and cardiac disorders; and Stage III, with chronic arthritis, psychiatric disorders, and a chronic fatigue syndrome.
Efficacy of staging is limited, however, because of the inconsistency of clinical manifestations among patients.

Further, stages may overlap with a mixture of both acute and chronic facets of the disease.

Lyme disease remains difficult to diagnose, in part because the causative agent, Borrelia burgdorferi, is usually not easily cultured or directly observable from patients' specimens. Currently available standard laboratory tests are not fully satisfactory in that they lack sensitivity and specificity and are not well standardized.

Underdiagnosis has proven to be a problem in parts of the country where it is not endemic or is relatively uncommon. Lyme disease can present with a wide variety of signs and symptoms, making it difficult for physicians who have little or no experience with it to make a correct diagnosis. On the other hand, in parts of the country where Lyme disease is well established and where there has been extensive publicity, patients with signs and symptoms suggestive of Lyme disease may be diagnosed inappropriately as having the disease when in fact they have some other disease resembling it.

Both aspects of this problem could be addressed by more sensitive, accurate, and inexpensive diagnostic tests. In general, serologic tests currently available do not detect some cases of early Lyme disease; conversely, in the later stages of the disease, tests are often too sensitive and less specific.

Once diagnosed, the manifestations of Lyme disease appear to be potentially treatable with a variety of antibiotics. The optimal regimen, including choice of drug, dose, route of administration, and length of therapy, has yet to be determined. Further clarification is also needed to determine the best method of treating disease sequelae at both early and late stages of Lyme disease.

Recent studies seem to indicate that tetracyclines or ceftriaxone may be superior to penicillin. Oral tetracycline administration is typically effective in treating early erythema migrans, but once arthritis or neurologic manifestations have developed, high-dose parenteral treatment is recommended, although the effect on neurologic symptoms has not yet been proven. In the absence of long-term observations, it is not clear that oral administration of drugs alone can effect a cure, prevent further complications, or forestall evolution to a chronic disease state.

RESEARCH GOALS AND SCOPE

The goal of this Request for Applications (RFA) is to stimulate research to effect better diagnosis and treatment of Lyme disease.

Applications submitted in response to this RFA are expected to concentrate upon: developing and testing methods of diagnosis that are more reliable, accurate, and sensitive than current techniques to detect Lyme disease in patients; and/or developing and testing improved ways to treat all aspects (arthritic, cardiac, neurologic, and so forth) and stages of the disease.

Specific issues that may be addressed include, but are not limited to:

Diagnosis:

- Classification and validation of clinical criteria;
- Proper identification of erythema migrans (in contrast to non-tick insect bites);
- Whether diagnostic criteria differ in children and adults;
- Optimal methods for serodiagnosis;
- The effect of therapy on serodiagnosis;
- The utility of various biological fluids and tissue for diagnosis;
- The best and most sensitive methods to detect spirochetal antigens;
- Differential diagnosis strategies.

Treatment:

- Drugs to be used in treating erythema migrans;
- Optimal treatments for arthritic, neurologic, cardiac, and other later manifestations of Lyme disease;
- Appropriate treatment of Lyme disease in children;
- Appropriate treatment of Lyme disease in pregnant women;
- Appropriate treatment of congenital Lyme disease;

o Utility of prophylactic antibiotics in exposed individuals from endemic areas.

MECHANISM OF SUPPORT

Applications considered appropriate responses to this RFA are the traditional research project grants (R01). Approximately $1,500,000 in total costs per year for 3 to 5 years will be committed by the NIAMS specifically to fund applications that are submitted in response to this RFA. Approximately seven awards are expected to be made for this RFA.

The funding level for this RFA is dependent on the receipt of a sufficient number of applications of high scientific merit. The total project period for applications submitted may not exceed five (5) years. The earliest possible start date for the initial awards will be September 30, 1991. Although there are provisions for this program in the financial plans of the NIAMS, award of grants pursuant to this RFA is contingent upon the availability of funds for this purpose. Applications may receive secondary assignment, when appropriate, to other institutes of the NIH. Non-profit and for-profit institutions, as well as foreign and domestic institutions, are eligible to apply.

This RFA is a one-time solicitation. Future unsolicited competing renewal applications that result from this current RFA will compete as research project applications with all other investigator-initiated applications and be reviewed by a standing Division of Research Grants study section.

In order to facilitate program planning and development, and to promote research interactions, the NIAMS intends to organize annual meetings of Principal Investigators and other key staff members of NIAMS-supported Lyme disease research projects. Funds for travel to these meetings (in Bethesda, Maryland) must be included in each year of the budget.

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH and ADAMHA policy is that applicants for NIH/ADAMHA clinical research grants and cooperative agreements will be required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis should be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are

excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale should be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information should be included in the form PHS 398 in Section 2, A-D of the Research Plan AND summarized in Section 2, E, Human Subjects. Applicants/offerors are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (i.e., Native Americans (including American Indians or Alaskan Natives), Asian/Pacific Islanders, Blacks, Hispanics).

The rationale for studies on single minority population groups should be provided.

For the purpose of this policy, clinical research includes human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including but not limited to clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the United States' populations, including minorities.

If the required information is not contained within the application, the application will be returned.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed AND the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

REVIEW PROCEDURES AND CRITERIA

REVIEW PROCEDURES

Applications will be reviewed initially by the Division of Research Grants for completeness and will be assigned to a special NIAMS review group. Evaluation for responsiveness to the RFA is an NIAMS program staff function. Applications that are judged non-responsive will be returned to the applicant but may be submitted as investigator-initiated applications at the next receipt date.

If the number of applications submitted is large compared to the number of awards to be made, the NIH will conduct an administrative review (triage) to eliminate those that are clearly not competitive. The NIH will withdraw from further competition those applications judged to be noncompetitive and notify the applicant and institutional business official.

Those applications judged to be both responsive and competitive will be evaluated in accordance with the criteria stated below for scientific/technical merit by an appropriate initial review group convened by the NIAMS Review Branch. The second level of review will be conducted by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

REVIEW CRITERIA

Applications responsive to this competitive solicitation will be reviewed in accordance with the following criteria:

1. Extent of relevance of the proposed research to the aims of the RFA.

2. Scientific merit of the proposed approach, including the accuracy and quality of the methodological approach and the research design. Familiarity with the proposed techniques should be demonstrated, e.g., by presentation of preliminary data.

3. Expertise and qualifications of the Principal Investigator and proposed staff and/or collaborators to perform the proposed research.

4. Documentation of the adequacy of the facilities and resources.

The review group will critically examine the proposed budget and recommend an appropriate budget for each approved application.

APPLICATION PROCEDURES

The research grant application form PHS 398 (revised 10/88) must be used in applying for these grants. This form is available at most institutional business offices and from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, Room 449, Westwood Building, 5333 Westbard Avenue, Bethesda, MD 20892.

The RFA label available in the 10/88 revision of form PHS 398 must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the title of the RFA and the RFA number must be typed on line 2 of the face page of the application form.

Submit a signed, typewritten original of the application, including the Checklist, and four (4) signed, exact photocopies, in one package to the Division of Research Grants at the address below. The photocopies must be clear and single-sided.

DIVISION OF RESEARCH GRANTS
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

At the time of submission, two (2) additional copies of the application must also be sent to:

REFERRAL OFFICER
Extramural Program
National Institute of Arthritis and Musculoskeletal and Skin
Diseases
Westwood Building, Room 5A-07
5333 Westbard Avenue
Bethesda, MD 20892

Applications must be received by June 17, 1991. If an application is received after that date it will be returned to the applicant.
If the application submitted in response to this RFA is substantially similar to a research grant application already submitted to the NIH for review, but has not yet been reviewed, the applicant will be asked to withdraw either the pending application or the new one. Simultaneous submission of identical applications will not be allowed, nor will essentially identical applications be reviewed by different review committees. Therefore, an application cannot be submitted in response to this RFA that is essentially identical to one that has already been reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent by May 1, 1991. This letter should include the name of the institution, any other participating institutions, the Principal Investigator and other key investigators, and a descriptive title. Such a letter of intent is not binding and will not enter into the review of any application subsequently submitted, nor is it a necessary requirement for application. Letters of intent are requested solely for review planning purposes. They allow NIAMS staff to estimate the potential review workload and to avoid possible conflict of interest in the review. NIAMS staff will not provide responses to such letters.
Letters of Intent are to be submitted to:

Dr. Tommy L. Broadwater
Chief, Grants Review Branch
Extramural Program
National Institute of Arthritis and Musculoskeletal and Skin
Diseases
Westwood Building, Room 5A-05A
Bethesda, MD 20892
Telephone: (301) 496-0754

INQUIRIES

Written and telephone inquiries concerning the objective and scope of this RFA and inquiries about whether specific proposed research would be responsive are encouraged and should be directed to:

Dr. Lawrence Petrucelli
Arthritis Program Director
National Institute of Arthritis and Musculoskeletal and Skin
Diseases
5333 Westbard Avenue
Westwood Building, Room 405
Bethesda, MD 20892
Telephone: (301) 496-7326

For fiscal and administrative matters, contact:

Diane M. Watson
Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 407-A
Bethesda, MD 20892
Telephone: (301) 496-7495

This program is described in the Catalog of Federal Domestic Assistance No. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research. Awards will be made under authorization of the Public Health Service Act, Title III, Section 301 (c) (Public Law 78-410, as amended; 42 USC 241) and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

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